

KFVGGAENTAHPRIISAPEMRQESEQGPCRRHMEASLQELKASPRMVPRAYVLPNC
DRKGFYKRKQCKPSRGRKRGICWCVDKYGMKLPGMEYVDGDFQCHTFDSSNVE
(SEQ ID NO: 49)

HTRISELKAEAVKKDRRKLTQS (SEQ ID NO: 50)

IGFBP-6

PQAGTARPQDVNRRDQQRNPGTSTTPSQPNSAGVQDTEMGPCRRHLDVQLQQLQTE
VYRGAQTLVVPNC DHRGFYRKRQCRSSQGQRRGPCWCVD RMGKSLPGSPDGNSS
SCPTGSSG (SEQ ID NO: 44),

and cyclic, glycosylated, phosphorylated, acetylated, amidated and/or sulfated
derivatives thereof.

REMARKS

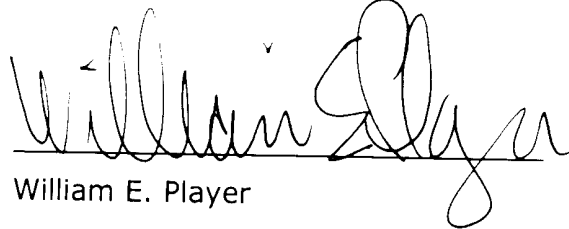
Claims 16-30 are pending.

The specification and claims (claim 16) are amended, hereby, to insert
the sequence identifiers set forth in the paper copy of the "Sequence Listing"
filed concurrently herewith.

Favorable action is requested.

Respectfully submitted,
JACOBSON-HOLMAN PLLC

By:

A handwritten signature in black ink, appearing to read "William E. Player", written over a horizontal line.

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Date: October 31, 2002

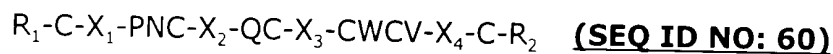
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MARKED UP VERSION ATTACHED TO AMENDMENT IN
SERIAL NO. 09/582,107

Marked up version of the paragraph starting at page 1, line 20, thru page 2, lines 1-10, is below:

Please delete the paragraph on page 1, line 20, thru page 2, lines 1-10, and replace it with the following paragraph:

Preferred peptides are peptides having an amino acid sequence of formula

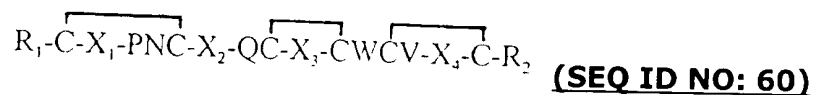


wherein

R_1 is NH_2 , an amino acid or a peptide having an amino acid sequence comprising up to 41 amino acids, X_1 is a peptide having an amino acid sequence comprising from 24 to 31 amino acids, X_2 is a peptide having an amino acid sequence comprising 9 amino acids, X_3 is a peptide having an amino acid sequence comprising 10 amino acids, X_4 is a peptide having an amino acid sequence comprising from 18 to 24 amino acids, R_2 is $COOH$, $CONH_2$ or a peptide having up to 12 amino acids, and cyclic, glycosylated, phosphorylated, acetylated, amidated, sulfated derivatives and or fragments thereof having the physiological activity of IGFBP.

Marked up version of the paragraph starting at page 2, lines 12-17, is below:

The peptides according to the invention can have disulfide bridges to correspond to the general formula:



In a preferred embodiment, the peptides have a glycine on one or more of the following positions of the amino acid sequence. X_2 on position 4, X_3 on position 9, X_4 on position 4 or 5, and/or X_4 on position 9 or 10.

Marked up version of the paragraph starting at page 15, lines 24-26, thru page 16, lines 1-11, is below:

The samples are applied to a Polybrene membrane in amounts of between 100 and 400 pmol. In accordance with the results of mass determinations, the following N-terminal sequences were found:

IGFBP-2-13, MW 12,681

(reduced molecule modified with iodoacetamide, MW 13,045)

Amino acids

GGKHHLGLEEPKKLRPPPARTPCQQELDQV... **(SEQ ID NO: 51)**

IGFBP-2-13, MW 12,865

(reduced molecule modified with iodoacetamide, MW 13,223)

Amino acids

GKGGKHHLGLEEPKKLRPPPARTPCQQELDQV... **(SEQ ID NO: 52)**

IGF-II, MW 7471

Amino acids

AYRPSETLCGGEL.... **(SEQ ID NO: 53)**

Marked up version of the paragraph starting at page 18, lines 22-24, is below:

The following N-terminal sequence was found:

IGFBP-4-11, MW 11,344 Da

KVNGAPREDARPVPQGSXQSELIIRALERL... **(SEQ ID NO: 54)**

Marked up version of the paragraph starting at page 19, lines 10-20, is below:

The analysis of the sulfur-bridge cross-linking was performed by cleaving the native peptide IGFBP-4-11 in two different parallel reactions with the endoproteases chymotrypsin and Arg-C. The cleaving fragments obtained were then separated by analytical reversed-phase chromatography and subjected to molecular mass and sequence analyses. The following fragments containing two cysteines and one sulfur bridge each were obtained:

HPKQCHPALDGQRGKCW (SEQ ID NO: 55), MW 1960

CVDRKTGVKLPGGLEPKGELDCHQLADSF (SEQ ID NO: 56), MW 3112

PVPQGSCQSELHR (SEQ ID NO: 57)

MW 3236

THEDLYIIPNCDR (SEQ ID NO: 58)

Marked up version of the paragraph starting at page 20, lines 25-26, thru page 21, lines 1-2, is below:

By a similar method to that used in Examples 1 and 3, a peptide could be isolated from hemofiltrate, having a mass of 2,470 Dalton (MALDI: 2481 Dalton) and the following sequence:

HTRISELKAEAVKKDRRKLTQS (?) (SEQ ID NO: 59)

from which the following sequence results as the C-terminal sequence of IGFBP-3:

KVDYESQSTDTQNFSSSESKRETEYGPCRREMEDTLNHLKFLNVLSPRGVHIPNCDKKGF
YKKKQCRPSKGRKRGFCWCVDKYGQPLPGYTTKGKEDVHCYSMQSK (SEQ ID NO: 46)

Marked up version of the paragraph starting at page 21, line 4-8, is below:

By a similar method to that used in Examples 1 and 3, the N-terminal domain of IGFBP-4 could be isolated, having the following sequence:

DEAIHCPPCSEELARCRPPVGCEELVREPGCGCCATCALGLGMPCGVYTPRCGSGRLRCYPPR
GVEKPLHTLMHGQGVCMEIAIEAIQESLQPSDKDEGDHPNNSFSPCSAHDRRCLQK
HFAKIRDRSTSGGKM **(SEQ ID NO: 48)**

Marked up version of the paragraph starting at page 21, lines 11-14, is
below:

By a method as in Examples 1 and 3, a peptide with a mass of 13.5 kD could be determined. The sequence determination gave the following sequence:

KFVGGAENTAHPRIISAPEMRQESEQGPCRRHMEASLQELKASPRMVPRVYLPNCDRKGFK
RKQCKPSRGRKRGICWCVDKYGMKLPMEYVDGDFQCHTFDSSNVE **(SEQ ID
NO: 49)**

Marked up version of claim 16 is below:

Please amend the claims as follows:

16. **(Amended)** Peptides, characterized in that said peptides are selected from

IBP-1

APSEEDHSILWDAISTYDGSKALHVTNIKKWKEPCRIELYRVVESLAKAQETSGEEISK
FYLPNCNKNGFYHSRQCETSMDGEAGLCWCVYPWNGKRIPGSPEIRGDPNCQIYFNV
QN **(SEQ ID NO: 39)**

IGFBP-2

GKGGKHHLGLEEPKKLRPPPARTPCQQELDQVLERISTMRLPDERGPLEHLYSLHIPNC
DKHGLYNLKQCKMSLNGQRGECWCVPNTGKLIQGAPTIRGDPECHLFYNEQQEARG
VHTQRMQ **(SEQ ID NO: 40)**

GGKHHLGLEEPKKLRPPPARTPCQQELDQVLERISTMRLPDERGPLEHLYSLHIPNCD
KHGLYNLKQCKMSLNGQRGECWCVPNTGKLIQGAPTIRGDPECHLFYNEQQEARGV
HTQRMQ **(SEQ ID NO: 45)**

IGFBP-3

GHAKDSQRYKVDYESQSTDTQNFSSSESKRETEYGPCRREMEDTLNHLKFLNVLSPRG
VHIPNCDKKGFYKKKQCRPSKGRKRGFCWCVDKYGQPLPGYTTKGKEDVHCYSMQS
K **(SEQ ID NO: 41)**

KVDYESQSTDTQNFSSSESKRETEYGPCRREMEDTLNHLKFLNVLSPRGVHIPN
CDKKGFYKKKQCRPSKGRKRGFCWCVDKYGQPLPGYTTKGKEDVHCYSMQSK
(SEQ ID NO: 46)

HPLHSKIIIIKKGHAKDSQRY **(SEQ ID NO: 47)**

IGFBP-4

DEAIHCPPCSEEKLARCRPPVGCEELVREPGCGCCATCALGLGMPCGVYTPRCGSLR
CYPGRGVEKPLHTLMHGQGVCMEIAIEAIQESLQPSDKDEGDHPNNSFSPCSAHDR
RCLQKHFAKIRDRSTSGGKM **(SEQ ID NO: 48)**

KVNGAPREDARPVPQGSCQSELHRALELAASQSRTHEDLYIIPNCDRNGNFHPKQ
CHPALDGQRGKCWCVDRKTGVKLPGGLEPKGELDCHQLADSFRE **(SEQ ID NO: 42)**

IGFBP-5

LTQSKFVGGAENTAHPRIISAPEMRQESEQGPCRRHMEASLQELKASPRMVPRAYLP
NCDRKGIFYKRKQCKPSRGRKRGICWCVDKYGMKLPMEYVDGDFQCHTFDSSNVE
(SEQ ID NO: 43)

KFVGGAENTAHPRIISAPEMRQESEQGPCRRHMEASLQELKASPRMVPRAYLPNC
DRKGFYKRKQCKPSRGRKRGICWCVDKYGMKLPMEYVDGDFQCHTFDSSNVE
(SEQ ID NO: 49)

HTRISELKAEAVKKDRRKLTQS **(SEQ ID NO: 50)**

IGFBP-6

PQAGTARPQDVNRRDQQRNPGTSTTPSQPNSAGVQDTEMGPCRRHLDSVLQQLQTE
VYRGAQTLYVPNCDHRGFYRKRQCRSSQGQRRGPCWCVDRMGKSLPGSPDGNGSS
SCPTGSSG **(SEQ ID NO: 44)**,

and cyclic, glycosylated, phosphorylated, acetylated, amidated and/or sulfated
derivatives thereof.